

Amendments to the Specification

Page 1, paragraph number [0006], please amend as follows:

[0006] A state of disorder of the intestinal system is in particular all intestinal disorders in which the epithelial layer is damaged, mostly as a result of malabsorption-diarrhoea diarrhea, also associated with dehydration.

Page 1, paragraph number [0007], please amend as follows:

[0007] Every year, the enteric pathogens are responsible for many neonatal calf deaths resulting in several \$100 million in losses to the agricultural economy of the world. Young calves are stressed by transportation, a change in environment and diet when weaned. Stress comes in many forms, however, the foremost effect of stress on the gastrointestinal tract is to decrease ~~mucosal~~ mucosal blood flow and thereby compromise the integrity of the mucosal barrier. An important part of the barrier function is to prevent transit of bacteria from the lumen through the epithelium. Stress may lead to development of diseases such as ~~diarrhoea~~ diarrhea, also known as scours, and is associated with the disruption of the gastrointestinal barrier in conjunction with a dehydration of the young animal. Local infections by bacteria and virus, exposure to toxins, physical insults and many systemic diseases lead to the disruption. The disruption may be mild and relatively easy to recover or it may be fatal. The structural features of the intestinal barrier, such as the villi which are part of the mucosa, can be totally destroyed and absent during the time of these states of disorder of the intestinal system. For example corona virus (*Cryptosporidium parvum*) and rota virus all cause destruction of the mature cells on the tips of the intestinal villus. Absorption of electrolytes and simple sugars is drastically lowered during such disorders, and

therefore the young animal suffers from the inability to absorb the nutrients and the water which it may consumes.

Page 1, paragraph number [0008], please amend as follows:

[0008] EP 0 160 015 describes a preparation for rehydrating monogastric animals, including human beings, and new-born ruminants suffering from ~~diarrhoea~~ diarrhea, comprising an absorbent intumescent agent, e.g. Isphagula Husk, electrolytes, glucose and lactose-decomposing enzyme(s). The preparation is especially suited for the treatment of non-infectious ~~diarrhoea~~ diarrhea and ~~diarrhoea-diarrhea~~ caused by rota and corona viruses. It is mentioned that Isphagula Husk shows a considerable ability to decompose lactose, and that experiments indicate that mucous produced by Isphagula Husk replaces the damaged mucous layer in the subjects suffering from intestinal infections in such a way that it acts as a bioadhesive polymer which may ~~enhance~~ enhance glucose absorption. Furthermore, the preparation is described as having inter alia a protective effect on the intestinal mucosa.

Page 1, paragraph number [0010], please amend as follows:

[0010] In "New therapies for calf ~~diarrhoea~~ diarrhea: Therapy and prevention for the new millennium", Elaine Hunt, North Carolina State University College of Veterinary Medicine, it is mentioned that glutamine may play a role in ~~diarrhoeal~~ diarrheal disease through several mechanisms, and that it plays a role in maintaining mucosal integrity of the gut, and in controlled situations also has been successful in increasing the recovery of the damaged intestinal mucosa. It has been found that glutamine has a direct effect on the absorption of solute in the calf intestine and glutamine is proposed to be a significant component of electrolyte solutions in the future for

treating calf ~~diarrhoea~~ diarrhea. Glutamine, in addition to sparing the intestinal mucosa during nutrient deprivation, has been found to increase the speed of recovery of damaged mucosa. When glutamine was combined with TGF alpha it stimulated recovery from ischemia/reperfusion injury and did the same in porcine rotavirus enteritis. Furthermore, it has been shown that glutamine stimulates glutamine-coupled Na⁺ absorption in the cells on the tips of the intestinal villus in a pig, and that glutamine stimulates water and electrolyte absorption much more than glucose. It is furthermore found that a glutamine transporter is present throughout the ileal villus in the calf, and therefore glutamine based oral electrolyte solutions should be more effective than glucose based solutions in osmotic ~~diarrhoeas~~ diarrheas in calves. Other substances besides glutamine are mentioned that may stimulate local proliferation of cells in the process of mucosal repair, such as arginine, prostaglandins and certain growth factors, which together with glutamine have been found to stimulate mucosal repair in in vitro studies.

Page 2, paragraph number [0013], please amend as follows:

[0013] In "Evaluation of a glutamine-containing oral rehydration solution for the treatment of calf ~~diarrhoea~~ diarrhea using an "Escherichia coli" model", Brooks et al, The Veterinary Journal 1997, 153, 163-170, several different compositions of ORS's (oral rehydration solutions) have been investigated for their beneficial effects on blood glucose and body weight for calves which had E. coli administered orally. A single amino acid is focused on, namely glutamine, which is described as having the potential to promote enteric sodium uptake, and being important in sustaining the villus form and function (referring to "Glutamine and preservation of gut integrity", Van der Hulst et al., Lancet 341, 1363-5 (1993)), and possibly also as supporting the integrity barrier and immune function in the intestine (referring to "Intestinal fuels: glutamine,

short-chain fatty acids and dietary fiber", Evans et al., Journ. Parenteral and Enteral Nutrition, 17, 47-55 (1992)). The results are consistent with a previous result: the ability of glutamine to stimulate both neutral and electrogenic sodium absorption. It is mentioned that one of the beneficial properties of glutamine is to sustain the effect of epidermal growth factor on intestinal mucosal cell proliferation (referring to "Glutamine is essential for epidermal growth factor-stimulated intestinal cell proliferation, Ko et al., Surgery, 114,147-54 (1993)).

Page 2 paragraph [0015], please amend as follows:

[0015] It is an object of the invention to provide an improved preparation for the treatment of monogastric animals, including human beings, suffering from ~~diarrhoea~~ diarrhea, in particular to provide an improved healing of the mucosa during ~~diarrhoea~~ diarrhea.

Page 2, paragraph [0018], please amend as follows:

[0018] It is an object of the present invention to provide an improved preparation for supplying nutrients to a monogastric animal, including human beings, suffering from ~~diarrhoea~~ diarrhea, in particular a young animal.

Page 3, paragraph [0027], please amend as follows:

[0027] The ~~diarrhoea~~ diarrhea may be all kinds of ~~diarrhoea~~ diarrhea, especially non-infectious ~~diarrhoea~~ diarrhea, malabsorption/maldigestive, osmotic ~~diarrhoea~~ diarrhea for example caused by Rotavirus and Corona "Cryptosporidium parvum" viruses which viruses all cause destruction of the mature cells on the tips of the intestinal villus. The preparation according to the invention

is suited for the treatment of any ~~diarrhoea~~diarrhea associated with a need for supplying nutrients to the cells in the intestinal.

Page 4, paragraph [0047], please amend as follows:

[0047] In one embodiment the preparation comprises at least one of the salts comprised by the electrolytes and is at least one of the salts that will replace at least one of the salts lost by ~~diarrhoea~~diarrhea. When administering a preparation according to the invention the salts lost by ~~diarrhoea~~diarrhea are provided by replaced salts comprised by the electrolytes in order to bring about both rehydration or stop dehydration.

Page 4, paragraph number [0051], please amend as follows:

[0051] In one embodiment the preparation comprises at least one filler, at least one taste corrigent, at least one ~~colouring~~coloring agent.

Page 4, paragraph number [0054], please amend as follows:

[0054] In one embodiment the preparation comprises a pharmaceutically acceptable ~~colouring~~coloring agent.

Page 4, paragraph number [0055], please amend as follows:

[0055] In one embodiment the preparation comprises the ~~colouring~~coloring agent FD&C RED #40.

Page 4, paragraph number [0056], please amend as follows:

[0056] In one embodiment the preparation comprises ~~alfa-tocopherol~~ alpha-tocopherol (natural vitamin E).

Page 4, paragraph number [0057], please amend as follows:

[0057] In one embodiment the preparation is composed of 27.16% Isphagula Husk, 10.66% of lactic yeast including glutamine, 19.75% of electrolytes which are made up of 3.30% potassium chloride, 7.08% sodium hydrogen carbonate, 4.85% sodium chloride, 3.45% trisodium citrate dihydrate, 1.07% magnesium hydroxide; 38.10% dextrose monohydrate, 0.87% nicotinamide, 0.30% flavouring agent, 0.20% silicium dioxide, 2.43% wheat flour, 0.03% ~~feed colouring~~ coloring agent, 0.50% ~~alfa-tocopherol~~ alpha-tocopherol (natural vitamin E), where the percent by weight is calculated on the basis of the finished preparation.

Page 4, paragraph number [0058], please amend as follows:

[0058] In one embodiment the preparation is used for the manufacture of a medicament for treating ~~diarrhoea~~ diarrhea.

Page 4, paragraph number [0060], please amend as follows:

[0060] Stress is almost always associated with mucosal erosions. The villi, which are a structural part of the mucosal barrier, may be disrupted to a lesser or larger extent during a state of disorder of the intestinal system such as during ~~diarrhoea~~ diarrhea. The health condition is worsened dramatically upon such disruption, as the absorption of nutrients in the intestinals does not function properly. Until healing of the villi has completed to an extent where absorption of substances has a positive effect on the overall condition of the animal, the animal will be in

critical state. It is therefore crucial for the recovery to be expedient, often a few hours are thought to be important. Healing requires that the epithelial cells on the margins of the defect proliferate, differentiate and migrate into the damaged area to restore the normal cellular architecture and function. The process of healing may be described as a process with positive feedback with the growing villi being gradually able to absorb more and more nutrient substances. A small positive effect in the early stage is thus believed to have a great effect on the overall time of recovery and hence on the chances of survival.

Page 4, paragraph number [0064], please amend as follows:

[0064] The agent comprising a combination of a rehydrant containing Isphagula Husk and a mixture comprising amino acids will be used for the treatment of ~~diarrhoea-diarrhea~~ among all offspring of ruminants as long as these are monogastric, and for the treatment of non-infectious ~~diarrhoea-diarrhea~~ and ~~diarrhoea-diarrhea~~ caused by rota and corona viruses among all other one-stomached animals, including humans.

Page 5, paragraph number [0091], please amend as follows:

[0091] 20% Protibel.

Composition of Rehydrant no. 1

| | |
|---|-----------|
| Ca ²⁺ | 4 mmol/l |
| Na ⁺ | 78 mmol/l |
| K ⁺ | 37 mmol/l |
| Cl ⁻ | 71 mmol/l |
| Bicarbonate (HCO ₃ ⁻), and propionate <u>propionate</u> (CH ₃ CH ₂ COO ⁻), and phosphate (PO ₄ ³⁻), total: | 48 mmol/l |
| Isphagula Husk | 21% |
| Protibel | 20% |

Page 8, paragraph number [0099], please amend as follows:

[0099] The preparation according to the invention may e.g. be composed as follows:

| | |
|--|---------|
| Dextrose monohydrate | 38.10% |
| Psyllium powder (Isphagula Husk) | 27.16% |
| Potassium chloride, KCl | 3.30% |
| Sodium Hydrogen Carbonate | 7.08% |
| Sodium Chloride, NaCl | 4.85% |
| Trisodium citrate dihydrate | 3.45% |
| Nicotinamide | 0.87% |
| Lactic yeast mixture with high contents of proteins, | 10.66% |
| B-vitamins and ascorbic acid including glutamine Flavouring agent (sweet peach) | 0.30% |
| Silicium dioxide | 0.20% |
| Wheat flour 2.43% FD&C RED #40 (feed colouring -coloring agent) | 0.03% |
| Magnesium hydroxide, MgOH | 1.07% |
| alfa-tocopherol -alpha-tocopherol(natural vitamin E) 60% | 0.50% |
| TOTAL | 100.00% |